In vitro activity of 20 antibiotics against Cupriavidus clinical strains

Clémence Massip, Mathieu Coullaud-Gamel, Cécile Gaudru, Lucie Amoureux, Anne Doléans-Jordheim, Geneviève Héry-Arnaud, Hélène Marchandin, Eric Oswald, Christine Segonds, Hélène Guet-Revillet

2 Sun J, Chen C, Cui CY *et al*. Plasmid-encoded *tet*(X) genes that confer high-level tigecycline resistance in *Escherichia coli*. *Nat Microbiol* 2019; **4**: 1457–64.

3 Chen C, Cui CY, Zhang Y *et al*. Emergence of mobile tigecycline resistance mechanism in *Escherichia coli* strains from migratory birds in China. *Emerg Microbes Infect* 2019; **8**: 1219–22.

4 Wang Y, Wang Y, Wu CM *et al*. Detection of the staphylococcal multiresistance gene *cfr* in *Proteus vulgaris* of food animal origin. *J Antimicrob Chemother* 2011; **66**: 2521–6.

5 Zhang Y, Lei CW, Wang HN. Identification of a novel conjugative plasmid carrying the multiresistance gene *cfr* in *Proteus vulgaris* isolated from swine origin in China. *Plasmid* 2019; **105**: 102440.

6 Chen Y, Lei C, Zuo L *et al*. A novel *cfr*-carrying Tn*7* transposon derivative characterized in *Morganella morganii* of swine origin in China. *J Antimicrob Chemother* 2019; **74**: 603–6.

7 Li R, Xie M, Dong N *et al*. Efficient generation of complete sequences of MDR-encoding plasmids by rapid assembly of MinION barcoding sequencing data. *Gigascience* 2018; **7**: 1–9.

8 Bie L, Wu H, Wang XH *et al*. Identification and characterization of new members of the SXT/R391 family of integrative and conjugative elements (ICEs) in *Proteus mirabilis*. *Int J Antimicrob Agents* 2017; **50**: 242–6.

9 Burrus V, Marrero J, Waldor MK. The current ICE age: biology and evolution of SXT-related integrating conjugative elements. *Plasmid* 2006; **55**: 173–83.

10 Burrus V, Waldor MK. Control of SXT integration and excision. *J Bacteriol* 2003; **185**: 5045–54.

J Antimicrob Chemother 2020; **75**: 1654–1658
doi:10.1093/jac/dkaa066
Advance Access publication 12 March 2020

In vitro activity of 20 antibiotics against *Cupriavidus* clinical strains

Clémence Massip[1,2], Mathieu Coullaud-Gamel[1,3], Cécile Gaudru[1,2], Lucie Amoureux[4,5], Anne Doleans-Jordheim[6,7], Geneviève Hery-Arnaud[8,9], Hélène Marchandin[10], Eric Oswald[1,2], Christine Segonds[11] and Hélène Guet-Revillet[1,2,11]*

[1]Service de Bactériologie-Hygiène, CHU de Toulouse, Toulouse, France; [2]IRSD, Université de Toulouse, INSERM, INRA, ENVT, UPS, Toulouse, France; [3]Lycée Stéphane Hessel, Toulouse, France; [4]Laboratoire de Bactériologie, CHU Dijon, Dijon, France; [5]UMR 6249 CNRS Chrono-environnement, Université de Bourgogne Franche-Comté, Besançon, France; [6]Laboratoire de Bactériologie, Instituts des Agents Infectieux, Centre de Biologie et Pathologie Nord, Hospices Civils de Lyon, Lyon, France; [7]Equipe de Recherche Bactéries Pathogènes Opportunistes et Environnement, UMR CNRS 5557 Ecologie Microbienne, Université Lyon 1 et VetAgro Sup, Villeurbanne, France; [8]Département de Bactériologie-Virologie, Hygiène et Parasitologie-Mycologie, Centre Hospitalier Régional Universitaire (CHRU) de Brest, Brest, France; [9]INSERM, EFS, UMR 1078 'Génétique, Génomique Fonctionnelle et Biotechnologies', Univ Brest, F-29200 Brest, France; [10]HydroSciences Montpellier, CNRS, IRD, Univ Montpellier, Département de Microbiologie, CHU Nîmes, Nîmes, France; [11]Observatoire Burkholderia cepacia, CHU de Toulouse, Toulouse/Vaincre la Mucoviscidose, Paris, France

*Corresponding author. E-mail: guet-revillet.h@chu-toulouse.fr

Sir,

Cupriavidus are Gram-negative non-lactose-fermenting motile bacilli with peritrichous flagella, a number of which were previously and successively classified in the *Ralstonia* and *Wautersia* genera. Until the recent expansion of MALDI-TOF MS, *Cupriavidus* could be mistaken for *Burkholderia* or *Pseudomonas* species. They are resistant to heavy metals and have been described from environmental (soil and water) samples, as well as from human samples.[1] *Cupriavidus gilardii*, *Cupriavidus pauculus* and *Cupriavidus metallidurans* are involved in invasive human infections, such as bacteraemia and pneumonia, most of which (though not exclusively) occur in immunocompromised patients.[2–4] Additionally, *Cupriavidus* species, *Cupriavidus respiraculi* in particular, are increasingly identified in patients

with cystic fibrosis (CF).[5] However, their clinical relevance in CF is not established. Due to the rare occurrence of *Cupriavidus* infections, antibiotic susceptibility data are only available from sparse case reports. Therefore, we determined the MICs of 20 antibiotics for a panel of *Cupriavidus* clinical strains, mainly from respiratory samples of CF patients (82%).

Thirty-seven epidemiologically unrelated clinical isolates of *Cupriavidus* obtained from the collection of the French Observatoire *Burkholderia cepacia* and from 11 French hospitals, as well as two type strains from clinical sources, i.e. *C. pauculus* LMG 3244^T and *C. respiraculi* LMG 21510^T (Laboratory of Microbiology, Ghent University, Ghent, Belgium),[1] were included. Isolates were identified by amplified ribosomal DNA restriction analysis (ARDRA)[6] and MALDI-TOF MS (Maldi Biotyper Microflex®, Bruker Daltonics, Bremen, Germany; IVD 7712). The experimental panel thus comprised 18 *C. respiraculi*, 6 *C. gilardii*, 5 *C. pauculus*, 4 *C. metallidurans*, 2 *Cupriavidus necator*, 2 *Cupriavidus taiwanensis*, 1 *Cupriavidus basilensis* and 1 unidentified *Cupriavidus* sp.

The MICs of 20 antibiotics, listed in Table 1, were determined using the broth microdilution method, as recommended by EUCAST (www.eucast.org). Briefly, each strain was inoculated on a blood agar plate (bioMérieux, Marcy-l'Étoile, France) for 16 h at 35°C. Bacterial suspensions in Mueller–Hinton broth (Bio-Rad, Marnes-la-Coquette, France) at concentrations of 5×10^5 cfu/mL were dispensed in 96-well microtitre plates (Dutscher, Brumath, France, 160 μL per well). Antimicrobial agents were added at increasing 2-fold concentrations (40 μL per well). The MICs were determined as the lowest antibiotic concentrations that inhibited visible bacterial growth after an 18 ± 2 h incubation at 35°C in an aerobic atmosphere. *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Staphylococcus aureus* ATCC 29213 were used as controls. All MICs were determined in triplicate and replicates never differed by more than 2-fold. For each MIC determination, the median of the replicates was recorded as the MIC. The MICs were interpreted according to *Pseudomonas* EUCAST breakpoints (2019) for colistin, amikacin and tobramycin, according to non-Enterobacteriaceae CLSI breakpoints (2019; https://clsi.org) for minocycline and co-trimoxazole and according to pharmacokinetic/pharmacodynamic (non-species-related) EUCAST breakpoints (2019) for the other antibiotics, except for temocillin, for which the previously proposed breakpoint of 16 mg/L was used.[7] The EUCAST and CLSI breakpoints that could be used to interpret *Cupriavidus* MICs are listed in Table S1 (available as Supplementary data at *JAC* Online).

The susceptibility testing results are summarized in Table 1 and the full MIC distributions of each tested antibiotic are available in Figure S1. Since *C. pauculus* and *C. metallidurans* are phylogenetically close species[1] and exhibited the same susceptibility profiles, they were considered as a group. Our collection comprises very few strains of *C. basilensis*, *C. necator*, *C. taiwanensis* and *Cupriavidus sp.* (maximum $n=2$ for each species). Moreover, these species have similar antibiotic susceptibility profiles, that's why they were also considered as a group. The susceptibility testing results interpreted with CLSI breakpoints are available in Table S2. The only significant change in our study between the EUCAST and CLSI interpretations concerned piperacillin/tazobactam. Eleven strains had an MIC of 8 or 16 mg/L (nine *C. respiraculi*). They were classified as susceptible to piperacillin/tazobactam according to CLSI breakpoints, but intermediate according to EUCAST breakpoints.

Nearly all strains were resistant to amoxicillin, amoxicillin/clavulanate, temocillin and aztreonam. Regarding cephalosporins, only 23% of *Cupriavidus* strains were ceftazidime susceptible, whereas 74% and 82% were susceptible to ceftriaxone or cefotaxime, respectively. The ceftolozane/tazobactam combination also demonstrated good activity, except against *C. gilardii*. For most strains, ceftazidime/avibactam MICs were similar compared with ceftazidime alone. Cefepime was the most active β-lactam, with 95% of strains being susceptible, whereas only a few strains were susceptible to meropenem (8%). Interspecies differences were observed for piperacillin/tazobactam and imipenem, since they were less active against *C. respiraculi* and *C. gilardii* than against the other species. Such discrepancies between meropenem and imipenem activities were previously noticed in case reports.[2,3] Similarly to *P. aeruginosa*, they could be due to the overexpression of efflux pumps from the resistance-nodulation-division family.[8] Indeed, a homologue of the MexAB OprM efflux pump that extrudes meropenem in *P. aeruginosa* has been identified in *C. gilardii*.[9]

Aminoglycosides were poorly active, in agreement with case reports,[2,3] probably due to efflux pumps and aminoglycoside-modifying enzymes.[9] Minocycline was the most active antibiotic, with very low MICs and a 100% susceptibility rate. Fluoroquinolones were frequently active, with over 80% of strains being susceptible, except for *C. pauculus and C. metallidurans*. Interspecies discrepancies were also noticed for co-trimoxazole. It was active against approximatively 80% of *C. gilardii* and *C. respiraculi* strains, whereas more than 50% of the strains belonging to other species were resistant.

Over 90% of *C. respiraculi* and 67% of *C. gilardii* strains were susceptible to colistin, while strains from the other species were mostly colistin-resistant. Colistin susceptibility was one of the characteristics of the *Cupriavidus* genus initially described by Vaneechoutte *et al.*[1] However, Petrou *et al.*[10] showed that the expression of ArnT was particularly strong in a strain of *C. metallidurans*. This enzyme catalyses the attachment of the cationic sugar 4-amino-4-deoxy L-arabinose (L-Ara4N) to lipid A phosphate groups. The subsequent reduction of negative membrane charge is responsible for colistin resistance. We detected homologues of *arnT* (CP000353.2: 1481129–1482725) using BLASTn in *C. basilensis*, *C. necator*, *C. pauculus* and *C. taiwanensis* sequenced strains (a query cover >80%, an identity >70% and an E value $<1 \times 10^{-40}$ were chosen as cut-off values for significance), which is in accordance with the high rate of colistin resistance in these species observed in our study. Additionally, *C. gilardii* appears to be the origin of the gene *mcr-5*, which is an emerging plasmid-mediated mechanism of colistin resistance in other environmental species such as *Salmonella* and *Pseudomonas*.[11]

In conclusion, our study showed that minocycline and cefepime exhibited the best *in vitro* activities against *Cupriavidus* strains. Meropenem, aminoglycosides and polymyxins, often considered antibiotics of last resort against infections caused by Gram-negative bacilli, do not have reliable activity against *Cupriavidus*. Perhaps resistance to these agents confers a selective advantage to *Cupriavidus* and therefore it may emerge in clinical scenarios where these agents are used, such as in patients with CF. Imipenem was more active than meropenem and cefotaxime/ceftriaxone was more active than ceftazidime. Ceftolozane/tazobactam had reasonable activity against *Cupriavidus*, whereas the novel inhibitor avibactam does not seem to add to the activity of

Table 1. MICs of 20 antibiotics for 39 *Cupriavidus* clinical strains, including two type strains, determined by the broth microdilution method

Bacteria (*n*)	Antibiotic	MIC (mg/L)		Percentage susceptible (breakpoint, mg/L)	Percentage resistant (breakpoint, mg/L)
		MIC_{50}	MIC_{90}		
Cupriavidus spp., all isolates (39)	amikacin	64	512	23 (≤8)	72 (>16)
	amoxicillin	512	>512	5 (≤2)	90 (>8)
	amoxicillin/clavulanate	256	>512	8 (≤2)	87 (>8)
	aztreonam	32	256	0 (≤4)	97 (>8)
	cefepime	1	4	95 (≤4)	0 (>8)
	cefotaxime	1	2	82 (≤1)	8 (>2)
	ceftazidime	16	32	23 (≤4)	54 (>8)
	ceftazidime/avibactam	8	32	69 (≤8)	31 (>8)
	ceftolozane/tazobactam	2	8	90 (≤4)	10 (>4)
	ceftriaxone	1	4	74 (≤1)	10 (>2)
	ciprofloxacin	0.125	1	74 (≤0.25)	18 (>0.5)
	colistin	2	16	56 (≤2)	44 (>2)
	co-trimoxazole	1	128	62 (≤2)	38 (>2)
	imipenem	2	8	69 (≤2)	21 (>4)
	levofloxacin	0.25	2	79 (≤0.5)	18 (>1)
	meropenem	32	64	8 (≤2)	74 (>8)
	minocycline	≤0.06	0.5	100 (≤4)	0 (>8)
	piperacillin/tazobactam	8	128	46 (≤4)	26 (>16)
	temocillin	32	512	31 (≤16)	69 (>16)
	tobramycin	256	>256	21 (≤4)	79 (>4)
C. respiraculi (18)	amikacin	128	512	6 (≤8)	89 (>16)
	amoxicillin	512	>512	0 (≤2)	100 (>8)
	amoxicillin/clavulanate	512	>512	0 (≤2)	100 (>8)
	aztreonam	32	32	0 (≤4)	100 (>8)
	cefepime	2	4	89 (≤4)	0 (>8)
	cefotaxime	1	2	78 (≤1)	11 (>2)
	ceftazidime	16	16	6 (≤4)	61 (>8)
	ceftazidime/avibactam	8	16	72 (≤8)	28 (>8)
	ceftolozane/tazobactam	2	4	94 (≤4)	6 (>4)
	ceftriaxone	1	4	67 (≤1)	17 (>2)
	ciprofloxacin	0.06	>16	83 (≤0.25)	17 (>0.5)
	colistin	1	2	94 (≤2)	6 (>2)
	co-trimoxazole	0.5	128	78 (≤2)	22 (>2)
	imipenem	2	8	61 (≤2)	22 (>4)
	levofloxacin	0.125	16	83 (≤0.5)	17 (>1)
	meropenem	64	64	0 (≤2)	83 (>8)
	minocycline	≤0.06	0.125	100 (≤4)	0 (>8)
	piperacillin/tazobactam	8	16	39 (≤4)	11 (>16)
	temocillin	32	32	50 (≤16)	50 (>16)
	tobramycin	>256	>256	6 (≤4)	94 (>4)
C. pauculus (5) and *C. metallidurans* (4)	amikacin	8	128	56 (≤8)	33 (>16)
	amoxicillin	256	512	0 (≤2)	78 (>8)
	amoxicillin/clavulanate	128	256	11 (≤2)	78 (>8)
	aztreonam	256	512	0 (≤4)	100 (>8)
	cefepime	0.5	1	100 (≤4)	0 (>8)
	cefotaxime	1	2	67 (≤1)	11 (>2)
	ceftazidime	8	16	33 (≤4)	44 (>8)
	ceftazidime/avibactam	8	16	78 (≤8)	22 (>8)
	ceftolozane/tazobactam	2	4	100 (≤4)	0 (>4)
	ceftriaxone	1	2	78 (≤1)	0 (>2)
	ciprofloxacin	0.5	1	44 (≤0.25)	44 (>0.5)

Continued

Table 1. *Continued*

Bacteria (*n*)	Antibiotic	MIC (mg/L)		Percentage susceptible (breakpoint, mg/L)	Percentage resistant (breakpoint, mg/L)
		MIC_{50}	MIC_{90}		
	colistin	16	32	0 (≤2)	100 (>2)
	co-trimoxazole	16	256	22 (≤2)	78 (>2)
	imipenem	0.25	2	100 (≤2)	0 (>4)
	levofloxacin	1	2	44 (≤0.5)	44 (>1)
	meropenem	16	64	11 (≤2)	67 (>8)
	minocycline	0.25	0.5	100 (≤4)	0 (>8)
	piperacillin/tazobactam	2	32	67 (≤4)	22 (>16)
	temocillin	256	512	0 (≤16)	100 (>16)
	tobramycin	64	128	44 (≤4)	56 (>4)
C. gilardii (6)	amikacin	64	128	0 (≤8)	100 (>16)
	amoxicillin	>512	>512	0 (≤2)	100 (>8)
	amoxicillin/clavulanate	>512	>512	0 (≤2)	100 (>8)
	aztreonam	128	128	0 (≤4)	100 (>8)
	cefepime	4	4	100 (≤4)	0 (>8)
	cefotaxime	1	1	100 (≤1)	0 (>2)
	ceftazidime	32	32	17 (≤4)	83 (>8)
	ceftazidime/avibactam	32	32	33 (≤8)	67 (>8)
	ceftolozane/tazobactam	8	16	50 (≤4)	50 (>4)
	ceftriaxone	1	2	67 (≤1)	17 (>2)
	ciprofloxacin	0.25	0.25	83 (≤0.25)	0 (>0.5)
	colistin	1	4	67 (≤2)	33 (>2)
	co-trimoxazole	1	1	83 (≤2)	17 (>2)
	imipenem	8	8	17 (≤2)	67 (>4)
	levofloxacin	0.25	0.25	100 (≤0.5)	0 (>1)
	meropenem	64	64	0 (≤2)	100 (>8)
	minocycline	0.125	0.125	100 (≤4)	0 (>8)
	piperacillin/tazobactam	128	128	0 (≤4)	83 (>16)
	temocillin	512	>512	0 (≤16)	100 (>16)
	tobramycin	256	>256	0 (≤4)	100 (>4)
C. basilensis (1), *C. necator* (2), *C. taiwanensis* (2) and *Cupriavidus* sp. (1)	amikacin	32	64	50 (≤8)	50 (>16)
	amoxicillin	32	256	33 (≤2)	67 (>8)
	amoxicillin/clavulanate	16	64	33 (≤2)	50 (>8)
	aztreonam	64	128	0 (≤4)	83 (>8)
	cefepime	≤0.25	≤0.25	100 (≤4)	0 (>8)
	cefotaxime	0.5	1	100 (≤1)	0 (>2)
	ceftazidime	4	8	67 (≤4)	17 (>8)
	ceftazidime/avibactam	4	8	83 (≤8)	17 (>8)
	ceftolozane/tazobactam	1	1	100 (≤4)	0 (>4)
	ceftriaxone	0.25	1	100 (≤1)	0 (>2)
	ciprofloxacin	0.125	0.25	83 (≤0.25)	0 (>0.5)
	colistin	16	16	17 (≤2)	83 (>2)
	co-trimoxazole	16	64	50 (≤2)	50 (>2)
	imipenem	0.25	2	100 (≤2)	0 (>4)
	levofloxacin	0.125	0.25	100 (≤0.5)	0 (>1)
	meropenem	8	16	33 (≤2)	33 (>8)
	minocycline	≤0.06	0.5	100 (≤4)	0 (>8)
	piperacillin/tazobactam	1	4	83 (≤4)	17 (>16)
	temocillin	128	512	50 (≤16)	50 (>16)
	tobramycin	64	64	50 (≤4)	50 (>4)

ceftazidime. Interspecies variations were observed, especially concerning colistin, co-trimoxazole, fluoroquinolones and piperacillin/tazobactam. Clinical data is now required to establish the optimal treatment of *Cupriavidus* infections.

Acknowledgements

We would like to thank Dr Aberrane from Créteil Hospital, Dr Belmonte from St Denis de La Réunion Hospital, Dr Dib from Troyes Hospital, Dr Ferroni from Paris University Hospital, Dr De Gialluly from Tours University Hospital and Dr Sansot from Toulon Hospital for providing the French Observatoire *Burkholderia cepacia* with *Cupriavidus* strains.

Funding

This study was supported by internal funding.

Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 and Figure S1 are available as Supplementary data at *JAC* Online.

References

1 Vaneechoutte M, Kämpfer P, De Baere T *et al*. *Wautersia* gen. nov., a novel genus accommodating the phylogenetic lineage including *Ralstonia eutropha* and related species, and proposal of *Ralstonia* [*Pseudomonas*] *syzygii* (Roberts *et al.* 1990) comb. nov. *Int J Syst Evol Microbiol* 2004; **54**: 317–27.

2 Bianco G, Boattini M, Audisio E *et al*. Septic shock due to meropenem- and colistin-resistant *Cupriavidus pauculus*. *J Hosp Infect* 2018; **99**: 364–5.

3 Kobayashi T, Nakamura I, Fujita H *et al*. First case report of infection due to *Cupriavidus gilardii* in a patient without immunodeficiency: a case report. *BMC Infect Dis* 2016; **16**: 493.

4 D'Inzeo T, Santangelo R, Fiori B *et al*. Catheter-related bacteremia by *Cupriavidus metallidurans*. *Diagn Microbiol Infect Dis* 2015; **81**: 9–12.

5 Coenye T, Spilker T, Reik R *et al*. Use of PCR analyses to define the distribution of *Ralstonia* species recovered from patients with cystic fibrosis. *J Clin Microbiol* 2005; **43**: 3463–6.

6 Segonds C, Paute S, Chabanon G. Use of amplified ribosomal DNA restriction analysis for identification of *Ralstonia* and *Pandoraea* species: interest in determination of the respiratory bacterial flora in patients with cystic fibrosis. *J Clin Microbiol* 2003; **41**: 3415–8.

7 Fuchs PC, Barry AL, Thornsberry C *et al*. Interpretive criteria for temocillin disk diffusion susceptibility testing. *Eur J Clin Microbiol* 1985; **4**: 30–3.

8 Pragasam AK, Raghanivedha M, Anandan S *et al*. Characterization of *Pseudomonas aeruginosa* with discrepant carbapenem susceptibility profile. *Ann Clin Microbiol Antimicrob* 2016; **15**: 12.

9 Ruiz C, McCarley A, Espejo ML *et al*. Comparative genomics reveals a well-conserved intrinsic resistome in the emerging multidrug-resistant pathogen *Cupriavidus gilardii*. *mSphere* 2019; **4**: e00631-19.

10 Petrou VI, Herrera CM, Schultz KM *et al*. Structures of aminoarabinose transferase ArnT suggest a molecular basis for lipid A glycosylation. *Science* 2016; **351**: 608–12.

11 Zhang H, Zong Z, Lei S *et al*. A genomic, evolutionary, and mechanistic study of MCR-5 action suggests functional unification across the MCR family of colistin resistance. *Adv Sci (Weinh)* 2019; **6**: 1900034.

J Antimicrob Chemother 2020; **75**: 1658–1660
doi:10.1093/jac/dkaa038
Advance Access publication 21 February 2020

Pharmacokinetics of once-daily doravirine over 72 h following drug cessation

Xinzhu Wang[1]*, Ana Milinkovic[2], Branca Pereira[2], Graeme Moyle[2], Serge Fedele[2], Lervina Thomas[2], Dilek Yener[2], Simon Connolly[2], Myra McClure[1] and Marta Boffito[1,2]

[1]Imperial College London, London, UK; [2]Chelsea and Westminster Hospital, London, UK

*Corresponding author. E-mail: xinzhu.wang@imperial.ac.uk

Sir,

Successful combination ART (cART) relies on daily adherence to cART.[1,2] The 'optimal' adherence pattern may be difficult to adopt as cART is for life and doses can be forgotten or delayed, making antiretrovirals with long half-lives ($t_{1/2}$s) desirable. Such drugs may allow for missed or delayed doses when drug concentrations are maintained at therapeutic levels until the next dose is administered.

Data on drug persistence and terminal $t_{1/2}$ are available for different cARTs and have been useful to advise clinicians and patients on delayed or missed doses.[3] Herein, we investigated the pharmacokinetic (PK) 'forgiveness' of the new NNRTI doravirine. Doravirine was recently approved to treat HIV infection as a single entity (Pifeltro®) and as a fixed-dose combination with tenofovir disoproxil fumarate and lamivudine (Delstrigo®).[4] Since the PK forgiveness of tenofovir disoproxil fumarate and lamivudine has been extensively studied,[5,6] in the present study we characterized the persistence of doravirine in the absence of other agents.

Regulatory and ethical approvals (London Westminster Research Ethics Committee 19/LO/0666) were obtained before initiating the study. Written informed consent was obtained from participants prior to study enrolment. In this Phase I, open-label, PK study, the participants received 100 mg of doravirine once daily for 7 days to